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(54) PREPARATIONS CONTAINING MICRO-ENCAPSULATED SUBSTANCES AND PROCESS FOR THEIR MANUFACTURE

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with dispersions, especially emulsions, containing micro-encapsulated substances and with a process for their manufacture.

The present invention provides a pharmaceutical preparation for topical administration (as hereinafter defined), in the form of a dispersion, which contains 1 to 40% by weight of water and a microencapsulated medicinally active substance.

The present invention also provides a process for the manufacture of a preparation according to the present invention, wherein the medicinally active substance is micro-encapsulated before being admixed with any ingredient of the remaining part of the dispersion.

The present invention is concerned especially with preparations for topical application containing microencapsulated medicinally active substances, in which the medicinally active substance or substances are chemically and physically stabilized by micro-encapsulation, and from which the said substances are released to the skin or mucous membrane at the desired speed depending on the wall material used for encapsulation. The invention is concerned, more especially, with preparations for topical application, which contain micro-encapsulated steroids.

The treatment of a very wide variety of skin diseases topically with dispersions containing medicinally active substances has been known. For this purpose the dispersion-like carrier for the medicinally active substance may be either of the type of a water-in-oil emulsion or of the type of an oil-in-water emulsion and is prepared in a known manner with the use of a very wide variety of auxiliary substances. All these dispersions contain, in addition to water, the medicinally active substance or substances subdivided in a molecularly to coarsely dispersed form as, for example, is described in United States Patent Specification No. 3,529,060.

It has been known that very many medicinally active substances present in the hitherto known dispersions described above exhibit a chemical and physical stability insufficient for a medicament. Thus, for example, in the various galenical formulations the medicinally active substances may decompose to a considerable extent even after short periods of storage. It has also been observed that medicinally active substances originally subdivided in a coarsely dispersed form partially dissolve in the emulsion base and during storage crystallize out in undesired crystal forms and particle sizes.

The present invention is based on the problem of, for example, galenically formulating medicament-containing emulsions capable of topical application, and, if desired, pleasing from a cosmetic point of view, in which the medicinally active substances, especially steroids, are chemically and physically stable and can also be liberated at the desired speed from the medicinal preparation to the skin or mucous membrane.

This problem has been solved in accordance with the present invention in such a manner that, for preparing, medicinal preparations in the form of dispersions containing medicaments having the desired chemical and physical stability, the medicaments are micro-encapsulated before being incorporated in the dispersion base.

It could not have been foreseen that the medicaments so encapsulated would come into action from the preparations when applied topically at the same speed and intensity as the corresponding non-encapsulated medicaments in the same preparations. This result is surprising, because it has been known that, when micro-encapsulated medicaments are used, the release of the medicament from the microcapsule takes place only in a retarded manner.

For making the medicinal preparations of

the present invention there are suitable all medicaments that have a solubility in water of at most 1%, and preferably up to 0.1%. These medicaments may belong to a very wide variety of groups of therapeutic substances, for example antiphlogistics, antibiotics, antimycotics, agents for the treatment of psoriasis and antipruriginosa, but especially antiphthlogistics. There may be mentioned for example, corticoids, for example 21 - trihydroxy - $\Delta^{1,4}$ - pregnadiene - 3,20 - dione (prednisolone) and esters thereof, 16α - methyl - 6α - fluoro - $\Delta^{1,4}$ 1 pregnadiene - 11β,21 - diol - 3,20 - dione (fluocortolone) and esters thereof, 9α - fluoro - hydrocortisone, $\Delta^{1,4}$ - dehydrocortisone (prednisolone), 9α - fluoro - 16α - hydroxy - prednisolone (triamcinolone) and derivatives thereof, 6α - methyl - prednisolone, 9α - fluoro - 16α - methyl prednisolone (dexamethasone) and derivatives thereof, 6α - fluoro - 9α - chloro - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 11β,21 - diol - 3,20 - dione clocortolone) and esters thereof, 9α - fluoro - 16β - methyl - prednisolone (betamethasone) and derivatives thereof, 6α,9α - difluoro - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 11β,21 - diol - 3,20 - dione (difluorocortolone) and esters thereof, 6α - fluoro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 21 - acid butyl ester, 6α,11β - difluoro - 9 - chloro - 21 - valeryloxy - 16α - methyl - $\Delta^{1,4}$ - pregnadiene 3,20 - dione, 6α - fluoro - 9,11β - dichloro - 21 - valeryloxy - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 3,20 - dione, 11 - dehydro - 17 - oxycorticosterone (cortisone), 11β,17α,21 - trihydroxy - Δ^4 - pregnene - 3,20 - dione (hydrocortisone) and esters thereof, and steroids such as, for example, Δ^4 - pregnene - 3,20 - dione (progesterone) and 1,2α - methylene - 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone (cyproterone) and esters thereof.

The microencapsulated medicaments may, however, also be, *inter alia*, antiseptics, for example 5,7 - dichloro - 8 - hydroxy - quinaldine (chloroquinaldine) and 5 - chloro - 8 - hydroxy - 7 - iodo - quinoline (vioform), antimycotics, for example 1 - (3 - iodo - 2 - propenyloxy) - 2,4,5 - trichloro - benzene (haloprogin) and nystatin, or antibiotics, for example chloramphenicol.

For micro-encapsulation any technological process may be used, in which an individual particle of, for example, a medicament or a limited number of particles of, for example, a medicament within a predetermined range of particle sizes is or are provided with a uniform protective coating. Especially suitable is the micro-encapsulation according to the process of micro-encapsulation by coacervation. In this case the wall material consists of gelatine, cellulose acetate phetalate or a styrene maleic acid copolymer, gelatine being the preferred wall material. The processes for micro-encapsulation with, for example, gelatine by simple or complex coacervation are known, *inter alia*, from United States Patent Specifications Nos. 2,800,457, 2,800,458, 3,317,434, 3,190,837, 3,533,958 and 3,341,466.

The micro-encapsulation of medicaments may also, if desired, be carried out by interfacial polymerization (for example United States Patent Specification No. 2,969,330), by interfacial polycondensation (for example United States Patent Specification No. 3,429,827) or by using mechanical processes of micro-encapsulation (for example United States Patent Specification No. 3,237,596). The wall material is so chosen that it is not soluble in the emulsion bases. The walls of the microcapsules may also be hardened by an after-treatment, and thus rendered less permeable to the micro-encapsulated medicament.

The term "dispersion" as used herein means an apparently homogeneous substance which comprises a microscopically heterogeneous mixture of two or more finely divided phases and includes a semi-solid preparation. The dispersion may, more especially, be an emulsion.

As auxiliary substances for formulating the dispersion bases there come into consideration all conventional and known toxically unobjectionable auxiliary substances, in which, for example, the medicament or medicaments are not appreciably soluble, for example paraffins, for example petroleum jelly, liquid paraffin and paraffin wax, fatty alcohols, for example cetyl alcohol, stearyl alcohol and myristyl alcohol, waxes, for example beeswax and spermaceti, fatty acid esters, *inter alia* fatty acid glycerides, glycols and glycol esters, emulsifiers and emulsion stabilizers.

The production of the medicament-containing dispersions may be carried out with the use of individual micro-encapsulated medicaments. Alternatively, combinations of several medicaments micro-encapsulated by different processes or combinations of micro-encapsulated and non-micro-encapsulated medicaments may be worked up. The non-micro-encapsulated medicaments may be present in the dispersion base subdivided either in a molecularly dispersed or coarsely dispersed form. It is possible, for example, for the dispersion to contain a medicament, a part of the medicament in the dispersion being micro-encapsulated and the remainder being non-micro-encapsulated.

If desired, other substances inert towards the medicament or medicaments, for example perfume oils, may be incorporated in the medicament-containing dispersions.

The incorporation of, for example, the micro-encapsulated medicaments used in the

dispersion base is advantageously carried out in a manner known *per se* by carefully stirring the microcapsules into the pre-made dispersions cooled to room temperature. When necessary, a suspension of microcapsules in a part of the auxiliary substances to be used for making the dispersion may be prepared, and then homogeneously dispersed by being carefully stirred into a previously prepared mixture of the remaining auxiliary substances, which mixture may be slightly heated to render it more stirrable.

The pharmaceutical preparations of the present invention which are for topical application may be in the form of lotions, creams, salves, ointments, sticks or suppositories; furthermore, such preparations may form part of a plaster. It is to be understood that the term "for topical application" is used herein to mean that the preparation is in a form of this kind and is not suitable for oral administration.

The following Examples illustrate the invention:—

Example 1

A salve for external use:

0.25 Gram of micronized * 6α - fluoro - 16α - methyl - 1 - dehydro - corticosterone caproate was triturated with 1.0 gram of paraffin oil (I). 0.30 Gram of 6α - fluoro - 16α - methyl - 1 - dehydrocorticosterone micro-encapsulated with gelatine (capsules having a diameter of about 10μm) having a content of active substance of 85% was uniformly dispersed by stirring in 5.0 grams of paraffin oil (II). Suspensions I and II were homogeneously dispersed in an emulsion base freshly prepared in the usual manner, cooled to 40°C, and consisting of 10.0 grams of Amphocerin E® (Firma Henkel/Dehydag), 10.0 grams of Cetiol V® (Firma/Henkel/Dehydag), 19.0 grams of paraffin oil, 20.0 grams of petroleum jelly and 34.45 grams of distilled water. *The term "Micronizer" is a registered Trade Mark (see also Example 15).

Example 2

A salve for external use:

0.60 Gram of 6α - fluoro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - $\Delta^{1,4}$ - pregnadiene 21 - acid butyl ester micro-encapsulated with gelatine, having a content of medicament of 80% and an average capsule size of 15 μm, was homogeneously dispersed in a water-in-oil emulsion freshly prepared in the usual manner, heated to about 30°C, and consisting of 5.0 grams of wool wax, 5.0 grams of beeswax, 20.0 grams of white petroleum jelly, 25.0 grams of Amphocerin K® (Firma Henkel/Dehydag), 14.4 grams of thickly liquid paraffin, 0.02 gram of Crematest® perfume oil No. 6580 (Firma Dragoco) and 29.98 grams of distilled water.

Example 3

A salve for external use:

0.25 Grams of prednisolone micro-encapsulated with polyethylene according to United States Patent Specification No. 3,161,602 and having a content of medicament of 70% was homogeneously dispersed, while stirring, in a water-in-oil emulsion heated to 35°C and prepared in the usual manner from 5.00 grams of beeswax, 5.00 grams of wool wax, 14.72 grams of thickly liquid paraffin, 20.00 grams of white petroleum jelly, 25.00 grams of Amphocerin K® (Firma Henkel/Dehydag), 30.00 grams of distilled water and 0.03 gram of perfume oil Chypre No. 6466 (Firma Haarmann & Reimer).

Example 4

A salve for external use:

0.30 Gram of 9α - fluoro - 16β - methyl - prednisolone micro-encapsulated with gelatine and having a content of active substance of 60% was homogeneously dispersed in a water-in-oil emulsion, which had been prepared in a known manner from 12.00 grams of Amphocerin E® (Firma Henkel/Dehydag), 7.00 grams of cetyl alcohol, 38.90 grams of white petroleum jelly, 17.00 grams of paraffin oil and 24.70 grams of distilled water with the addition of 0.10 gram of perfume oil Chrype No. 6466 (Firma Haarmann & Reimer).

Example 5

A cream for external use:

0.50 Gram of 6α - fluoro - 16α - methyl - 1 - dehydro - corticosterone micro-encapsulated with gelatine, having a content of active substance of 75% and an average capsule size of 10 μm, was homogeneously dispersed in an oil-in-water emulsion prepared in the usual manner, heated to 30°C, and consisting of 42.50 grams of paraffin oil, 3.00 grams of polyoxyl - 40 - stearate, 8.00 grams of Lanette O® (Firma Henkel/Dehydag), 15.00 grams of petroleum jelly, 1.00 gram of polyvinyl alcohol and 30.00 grams of distilled water.

Example 6

A salve for external use:

0.25 Gram of hydrocortisone micro-encapsulated with gelatine, having a content of active substance of 70% and an average particle size of 15 μm, was homogeneously dispersed in a water-in-oil emulsion heated to 35°C and having a composition as described in Example 3.

Example 7

A salve for external use:

0.30 Gram of 6α - fluoro - 9α - chloro - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 11β,21 - diol - 3,20 - dione micro-encapsulated with gelatine, having a content of active sub-

stance of 85% and an average particle size of 20 μm, was uniformly dispersed, while stirring, in 5.00 grams of paraffin oil (I). 0.25 Gram of chloramphenicol was triturated with 1.00 gram of paraffin oil (II). Suspensions I and II were homogeneously dispersed in a freshly prepared emulsion base cooled to 40° and having a composition as given in Example 1.

Example 8

A salve for external use:

The salve had the composition given in Example 7, except that it contains clemizol hexachlorophenate instead of chloramphenicol.

Example 9

A salve for external use:

5.00 Grams of micronized azauridin triacetate were triturated with 7.00 grams of paraffin oil (I). 0.40 Gram of 6α,9α - difluoro - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 11β,21 - diol - 3,20 - dione micro-encapsulated with gelatine, having a content of active substance of 80% and an average particle size of 14 μm, was uniformly dispersed in 1.98 grams of paraffin oil (II). The suspensions I and II were stirred one after the other into an emulsion base cooled to room temperature and consisting of 44.60 grams of petroleum jelly, 6.00 grams of beeswax, 5.00 grams of pentaerythritol fatty acid ester, 0.02 gram of perfume oil and 30.00 grams of distilled water.

Example 10

A cream:

0.50 Gram of progesterone micro-encapsulated with gelatine, having a content of active substance of 75% and an average capsule size of 10 μm, was homogeneously dispersed in an emulsion base having a composition as described in detail in Example 5.

Example 11

A cream:

0.50 Gram of 1,2α - methylene - 6 - chloro - 6 - dehydro - 17α - hydroxy - progesterone acetate micro-encapsulated with gelatine, having a content of active substance of 85% and an average capsule size of 15 μm, was homogeneously dispersed in an emulsion base having a composition as described in detail in Example 5.

Example 12

A salve:

0.40 Gram of 6α - fluoro - 9,11β - dichloro - 21 - valeryloxy - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 3,20 - dione micro-encapsulated with gelatine, having a content of active substance of 65% and an average capsule size of 16 μm, was suspended in 2.50 grams of paraffin oil (I). 1.00 Gram of 5,7 - dichloro - 8 - hydroxy - quinaldine was likewise suspended in 2.50 grams of paraffin oil (II). Suspensions I and II were homogeneously dispersed in an emulsion salve base prepared in a known manner from 12.00 grams of Lanette N® (Firma Henkel/Dehydag), 8.00 grams of Cetoil V® (Firma Henkel/Dehydag), 28.60 grams of distilled water, 25.00 grams of petroleum jelly and 20.00 grams of lanolin (Deutsches Arzneibuch, 7th edition).

Example 13

A cream:

1.50 Grams of 1 - (3 - iodo - 2 - propenyloxy) - 2,4,5 - trichlorobenzene micro-encapsulated with gelatine, having a content of active substance of 75% and an average capsule size of 20 μm, were uniformly dispersed, while stirring, in an oil-in-water emulsion base heated to 35°C and prepared in a known manner from 41.50 grams of paraffin oil, 3.00 grams of polyoxyl - 40 - stearate, 8.00 grams of Lanette O® (Firma Henkel/Dehydag), 15.00 grams of petroleum jelly, 1.00 gram of polyvinyl alcohol and 30.00 grams of distilled water.

Example 14

A haemorrhoidal salve:

0.40 Gram of 6α,11β - difluoro - 9 - chloro - 21 - valeryloxy - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 3,20 - dione micro-encapsulated with gelatine, having a content of active substance of 85% and an average capsule size of 15 μm, was suspended in 4.00 grams of paraffin oil (I). 0.50 Gram of cinchocaine hydrochloride, very finely ground, and 1.00 gram of micronized clemizal undecylate were triturated with 6.00 grams of paraffin oil (II). Suspensions I and II were mixed with a salve base prepared in a known manner from 60.00 grams of paraffin oil, 10.00 grams of Eutanol G®, 8.00 grams of hydrogenated castor oil, 7.50 grams of polyethylene glycol - 400 - monoricinoleate and 2.50 grams of distilled water with the addition of 0.10 gram of perfume oil.

Example 15

Suppositories:

0.30 Gram of 6α - fluoro - 16α - methyl - 1 - dehydro - corticosterone micro-encapsulated with gelatine, having a content of active substance of 85% and an average capsule size of 8 μm, 0.10 gram of cinchocaine hydrochloride, very finely ground, and 0.50 gram of micronized clemizol undecylate were worked up in a known manner with 90.00 grams of Adeps solidus (Deutches Arzneibuch, 7th edition) and 0.1 grams of distilled water to form a suppository composition, from which suppositories each weighing 2.00 grams were formed.

Example 16

Plasters:

As carrier material there was used a colourless soft PVC foil. There was applied to this foil a priming composition consisting of aluminium oxide (1.0 gram/m²), Perbunan®-latex (1.5 grams/m²) and natural rubber latex (1.5 grams/m²). Upon the latter was applied the adhesive composition proper that contained, in addition to 6α - fluoro - 16α - methyl - 1 - dehydro - corticosterone micro-encapsulated with gelatine and having a content of active substance of 80% and an average capsule size of 10 μm (0.25 gram/m²), azauridin triacetate (5 gram/m²), natural rubber (20.0 grams/m²), rosin ester (22.0 grams/m²), wool fat (7.0 grams/m²), distilled water 1.0 gram/m²) and an anti-aging agent (0.5 gram/m²).

Example 17

A medicinal stick for topical application:

0.60 Gram of 6α - fluoro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - $\Delta^{1,4}$ - pregnadien - 21 - acid butyl ester micro-encapsulated with gelatine, having a content of medicinally active substance of 80% and an average capsule size of 10 μm, was homogeneously suspended in a stick base prepared in a known manner from 4.90 grams of cetyl alcohol, 25.40 grams of beeswax, 19.60 grams of spermaceti, 17.00 grams of paraffin oil, 22.00 grams of a polyol fatty acid ester mixture (Cetiol He®, Firma Henkel/Dehydag) and 10.00 grams of distilled water with the addition of 0.50 gram of perfume oil. The medicament-containing stick composition was shaped into medicinal sticks each weighing 5.00 grams, and packed in casings having a retractable core.

Example 18

A salve for external use:

0.30 Gram of 6α - fluoro - 9α - chloro - 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 11β,21 - diol - 3,20 - dione micro-encapsulated with gelatin, having a content of active substance of 85% and an average particle size of 20 μm, was uniformly dispersed in 5.00 grams of paraffin oil. 0.25 Gram of chloramphenicol micro-encapsulated in accordance with United States Patent Specification No. 3,161,602 having a content of active substance of 70% was uniformly dispersed in 1.00 gram of paraffin oil. The two suspensions were homogeneously dispersed in a freshly prepared emulsion base cooled to 40°C and having a composition as given in Example 1.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation for topical administration (as hereinbefore defined), in the form of a dispersion, which contains 1 to 40% by weight of water and micro-encapsulated medicinally active substance.

2. A preparation as claimed in claim 1, wherein the medicinally active substance is an antiphlogistic, an antibiotic, an antimycotic or an antiseptic.

3. A preparation as claimed in claim 1, wherein the medicinally active substance is a steroid.

4. A preparation as claimed in claim 2 or claim 3, containing two or more medicinally active substances, each being in a micro-encapsulated form.

5. A preparation as claimed in any one of claims 1 to 3, containing a medicinally active substance in a micro-encapsulated form and a medicinally active substance in a non micro-encapsulated form.

6. A preparation as claimed in claim 5, wherein the medicinally active substances are the same substance.

7. A preparation as claimed in any one of claims 1 to 6, wherein the substance is micro-encapsulated in gelatine.

8. A preparation as claimed in any one of claims 1 to 7, wherein the substance has a solubility of up to 0.1% in water at room temperature.

9. A preparation as claimed in any one of claims 1 to 8, containing 2 to 30% by weight of water.

10. A preparation as claimed in any one of claims 1 to 9, which is in the form of a liquid.

11. A preparation as claimed in any one of claims 1 to 9, which is in the form of a semi-solid.

12. A preparation as claimed in any one of claims 1 to 9, which is in the form of a lotion, cream, ointment or stick.

13. A preparation as claimed in any one of claims 1 to 6 and 7 to 9, which is in the form of a salve or suppository.

14. A preparation as claimed in any one of claims 1 to 6 and 7 to 9, which forms part of an adhesive plaster.

15. A preparation as claimed in claim 1 and having a composition substantially as described in any one of Examples 1 to 18 herein.

16. A process for the manufacture of a preparation as claimed in any one of claims 1 to 15, wherein the substance is micro-encapsulated before being admixed with any

ingredient of the remaining part of the emulsion.

17. A process as claimed in claim 16, conducted substantially as described in any one of Examples 1 to 18 herein.

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